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A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland)

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High dietary intakes of calcium and dairy products have been hypothesized to enhance prostate cancer risk, but available prospective data regarding these associations are inconsistent. We examined dietary intakes of calcium and dairy products in relation to risk of prostate cancer in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, a cohort of 29,133 male smokers aged 50–69 years at study entry. Dietary intake was assessed at baseline using a validated 276-item food use questionnaire. Cox proportional hazards regression was used to adjust for known or suspected risk factors for prostate cancer. During 17 years of follow-up, we ascertained 1,267 incident cases of prostate cancer. High *versus* low intake of dietary calcium was associated with a marked increase in prostate cancer risk. The multivariate relative risk (RR) of prostate cancer for ≥2,000 mg/day compared to <1,000 mg/day of calcium intake was 1.63 (95% confidence interval (CI), 1.27–2.10; *p* trend < 0.0001). Total dairy intake was also positively associated with risk of prostate cancer. The multivariate RR of prostate cancer comparing extreme quintiles of intake was 1.26 (95% CI, 1.04–1.51; *p* trend = 0.03). However, no association with total dairy intake remained after we adjusted for calcium (*p* trend = 0.17). Findings were similar by stage and grade of prostate cancer. The results from this large prospective study suggest that intake of calcium or some related component contained in dairy foods is associated with increased prostate cancer risk.
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Key words: dietary calcium; dairy products; prostate cancer

Increased calcium and dairy product consumption has been suggested to enhance risk of prostate cancer,[1] with possible biological mechanisms including the propensity of high calcium intake to decrease serum levels of vitamin D, and the potential for dairy products to increase serum levels of insulin-like growth factor I (IGF-I).[2,3] Calcium is an important ingredient of dairy foods, yet previous epidemiological studies regarding the association between calcium and prostate cancer have yielded inconsistent results. High intake of calcium was reported to increase prostate cancer risk in several cohort studies (reviewed in Gao *et al.*[4]) and 1 case-control study.[5] In these investigations, the increase in risk was seen with both dietary[5–13] and supplemental calcium,[7,8,10,14] and was greater for advanced than for localized tumors.[5,7,8,12,14] By contrast, a small clinical trial evaluating the effect of calcium supplementation on prostate cancer incidence as a secondary outcome suggested a decreased prostate cancer risk in the calcium-treated group compared to the control group.[15]

In a previous report from the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, we reported that men with lower calcium and higher phosphorus intakes may be at decreased risk of prostate cancer.[16] That report was based on 8 years of follow-up and 184 cases of prostate cancer.[16] We now extend those initial findings to include 17 years of follow-up and 1,267 prostate cancer cases, and to investigate in detail dairy product consumption, calcium and other components of dairy products such as phosphorus, vitamin D and dairy fat that are positively correlated with calcium. We also examined whether the associations between intakes of calcium and dairy products and prostate cancer differed by stage and grade of the disease, and according to whether the cases were detected through clinical symptoms. These analytic approaches allowed us to explore important potential sources of detection bias that might not have always been adequately addressed in previous studies of calcium/dairy and prostate cancer. The ATBC study was conducted in Finland, which is characterized by high dairy product consumption[17] and therefore provides an ideal setting for examining these associations.

Material and methods

Study population

The Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study was a randomized, double blind, placebo controlled, 2 by 2 factorial design, primary prevention trial that tested whether daily supplementation with β-carotene (20 mg) and/or α-tocopherol (50 mg) reduced the incidence of lung cancer in male smokers recruited from southwestern Finland between 1985 and 1988. The ATBC study cohort consisted of 29,133 Caucasian men, between 50 and 69 years of age, who smoked 5 or more cigarettes per day at baseline. Men were excluded if they had a previous history of cancer (other than nonmelanoma skin cancer or carcinoma *in situ*) or other serious disease that limited long-term participation; used vitamin E, vitamin A or β-carotene supplements in excess of predefined doses; or used treatment with anticoagulants. The trial ended on April 30, 1993, with registry-based follow-up continuing thereafter. The rationale, design, methods, compliance and initial results of the ATBC study have been published elsewhere.[18,19] The present analysis is based on 27,028 cohort participants with complete baseline dietary, physical activity and anthropometric information. The study was approved by the institutional review boards of both the National Public Health Institute in Finland and the National Cancer Institute in the United States.

Prostate cancer case identification

Prostate cancer cases were identified through the Finnish Cancer Registry, which provides virtually 100% case coverage.[20] For cases diagnosed through April 1999, the medical records were reviewed by 2 study oncologists to confirm diagnosis and stage. One or 2 pathologists reviewed the histopathologic and cytologic specimens to confirm cancer and histologic type. Histological grade data were available for most of the cases (n = 817) that occurred before April 1999. For 864 cases, we also had information regarding whether their prostate cancers were detected

Abbreviations: ATBC, α-tocopherol, β-carotene cancer prevention study; BMI, body mass index; CI, confidence interval; PSA, prostate specific antigen; RDA, recommended daily allowance; RR, relative risk; TNM, tumor-node-metastasis; VDR, vitamin D receptor.

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TABLE I – BASELINE CHARACTERISTICS ACCORDING TO INCREASING CATEGORIES OF DIETARY CALCIUM INTAKE IN THE ATBC STUDY

Characteristics	Dietary calcium intake (mg/day)				
	<1000	1000–1499	1500–1999	≥2000	*p* trend
Age (years)	56.5	56.7	56.7	57.1	<0.0001
Body mass index (kg/m^2)	26.1	26.1	26.5	27.3	<0.0001
Height (cm)	174.2	173.7	173.4	173.4	<0.0001
Family history of prostate cancer (%)	2.1	2.2	2.2	2.3	0.44
History of type II diabetes (%)	2.7	3.5	5.3	7.5	<0.0001
Education > elementary (%)	25.5	23.5	17.7	19.1	<0.0001
Married (%)	19.5	18.5	18.5	21.2	0.21
Urban residence (%)	46.7	44.8	38.1	37.2	<0.0001
Physical activity at leisure (%)	57.8	59.0	58.4	56.3	0.36
Physical activity at work (%)	60.6	58.6	56.7	56.0	<0.0001
Smoking (no. of cigarettes per day)	21.3	20.3	20.1	20.8	0.44
Mean intakes per day					
Total energy intake (kcal)	3049	2701	2801	3156	0.02
Total fat (g)	101.8	105.2	107.2	109.7	<0.0001
Lycopene (μg)	833.2	823.7	738.1	746.7	<0.0001
α-Linolenic acid (μg)	1863.3	1726.0	1566.7	1428.5	<0.0001
Phosphorus (mg)	1800.9	2083.7	2337.4	2670.9	<0.0001
Calcium from food sources (mg)	789.6	1271.0	1697.3	2293.6	<0.0001
Calcium from dairy (mg)	461.6	954.7	1396.8	2015.4	<0.0001
Total dairy (g)	351.7	719.1	1038.0	1382.3	<0.0001
Dairy fat (g)	49.1	57.2	63.8	71.0	<0.0001
Dietary Vitamin D (μg)	5.8	5.5	5.3	5.0	<0.0001
Dietary Vitamin E (mg)	13.3	12.3	11.4	10.5	<0.0001
Fish (g)	40.7	39.8	39.0	35.8	<0.0001
Selenium (μg)	83.9	88.9	92.3	97.8	<0.0001
Red meat (g)	157.9	148.6	140.3	130.4	<0.0001
Alcohol (g)	26.3	18.5	14.3	12.7	<0.0001
Folate (μg)	336.2	337.1	337.8	338.3	0.08

All variables are directly standardized to the age distribution of the cohort; nutrients are adjusted for total energy intake by the residuals method.

through routine screening procedures or *via* clinical symptoms. Sixty-five percent of cases for whom such data were available ($n = 561$) were discovered because of prostate cancer symptoms.

Our main analysis is based on 1,267 incident prostate cancer cases. We also considered as separate endpoints nonadvanced, advanced, low grade and high grade prostate cancers. Nonadvanced cases ($n = 561$) were those with Stages 0–II and advanced cases ($n = 301$) were those with stages III or IV based on the tumor-node-metastasis (TNM) classification. Low grade cases ($n = 626$) were those with Grades 1 or 2 and high grade cases ($n = 191$) were those with Grades 3 or 4. Cases that occurred between May 1999 and April 2002 were ascertained using the Finish Cancer Registry[20]; stage and grade information were unavailable for these cases.

Baseline data collection

At baseline, subjects were asked to provide detailed demographic, medical and smoking information. Height and weight were measured by registered nurses. Participants were requested to complete a 276-item food use questionnaire reporting their portion size and frequency of consumption of foods and beverages within the past 12 months. A color picture booklet was provided to each participant to assist with portion size estimation. Nutrient intakes were calculated using the food composition database of the National Public Health Institute in Finland. The intraclass correlation coefficients between repeated administrations of the food use questionnaire spaced 3 months apart in a sample of $n = 133$ subjects ranged from 0.6 to 0.7 for most dietary variables including calcium. The correlation coefficients adjusted for intraindividual variation comparing the food use questionnaire with food records were 0.58 for vitamin D and 0.64 for calcium.[21]

Statistical analysis

Person-years of follow-up were calculated from the date of randomization until diagnosis of prostate cancer, death, or April 30, 2002. Baseline characteristics according to categories of calcium intake were determined and compared using the general linear models procedure in SAS, adjusting for age at randomization. Data on nutrient intake were log transformed and adjusted for total energy intake using the residuals method.[22] Cox proportional hazards regression[23] with person-years as the underlying time metric, was used to estimate relative risks (RR) and 95% confidence intervals (CI) for the association between intakes of calcium and dairy products and prostate cancer with the lowest intake category serving as the reference group. Because calcium intake in the Finnish population results mainly from dietary, not supplement intake,[16] we focused on dietary calcium. We divided calcium intake into 4 categories (<1,000, 1,000–1,499, 1,500–1,999, and ≥2,000 mg/day). In an alternative analysis, we divided calcium intake into quintiles, based on the distribution of calcium intake in the cohort. Total and individual dairy food intakes were also divided into quintiles, including total milk, whole milk, low fat milk, butter, ice cream, cream, cheese and sour milk products, which together capture total dairy product consumption. We also created a variable that represented calcium from dairy products. Because of the high correlation between dietary calcium and phosphorus (correlation coefficient $r = 0.86$), we derived variables representing calcium-adjusted phosphorus and phosphorus-adjusted calcium using the residuals method.[22] Tests for linear trend were obtained by assigning to each nutrient category the median value, treating this as a continuous variable, and evaluating the coefficient using the Wald test. We ran a restricted cubic regression spline with 4 knots (at 5, 25, 75 and 95%) to evaluate whether the association between dietary calcium and prostate cancer was linear and found no evidence for nonlinearity ($\Delta = 1.714$, 2 df; $p = 0.42$).

The multivariate models were adjusted for age at baseline and trial intervention group (β-carotene, α-tocopherol, both, placebo), and then additionally adjusted for physical activity, history of type II diabetes, family history of prostate cancer, height, body mass index (BMI), smoking inhalation, total number of cigarettes/day, marital status, education, urban residence and total energy intake.

TABLE II – RELATIVE RISK (95% CI) OF STAGE (NONADVANCED AND ADVANCED) AND GRADE (LOW AND HIGH) OF PROSTATE CANCER IN RELATION TO DIETARY CALCIUM INTAKE

Dietary calcium intake (mg/day)	Cases	Person-years	Minimal model RR[1]	Multivariate model RR[2]
Total prostate cancer				
<1,000	151	52,246	1.0	1.0
1,000–1,499	611	160,913	1.26 (1.05–1.50)	1.28 (1.07–1.54)
1,500–1,999	402	99,862	1.32 (1.10–1.59)	1.38 (1.14–1.67)
≥2,000	103	22,562	1.58 (1.23–2.03)	1.63 (1.27–2.10)
p trend			*0.0003*	*<0.0001*
Nonadvanced prostate cancer[3]				
<1,000	72	51,444	1.0	1.0
1,000–1,499	267	157,113	1.14 (0.88–1.47)	1.14 (0.87–1.48)
1,500–1,999	173	97,264	1.15 (0.87–1.52)	1.17 (0.89–1.55)
≥2,000	49	21,911	1.53 (1.07–2.20)	1.59 (1.10–2.29)
p trend			*0.05*	*0.03*
Advanced prostate cancer[3]				
<1,000	38	50,929	1.0	1.0
1,000–1,499	146	155,957	1.20 (0.84–1.72)	1.24 (0.86–1.78)
1,500–1,999	97	96,705	1.26 (0.86–1.83)	1.34 (0.91–1.95)
≥2,000	20	21,716	1.21 (0.70–2.07)	1.25 (0.73–2.16)
p trend			*0.35*	*0.23*
Low grade[4]				
<1,000	87	51,563	1.0	1.0
1,000–1,499	300	157,347	1.07 (0.84–1.36)	1.06 (0.84–1.36)
1,500–1,999	187	97,303	1.05 (0.81–1.35)	1.07 (0.83–1.39)
≥2,000	52	21,890	136 (0.97–1.92)	1.43 (1.01–2.02)
p trend			*0.19*	*0.10*
High grade[4]				
<1,000	23	50,790	1.0	1.0
1,000–1,499	94	155,624	1.26 (0.80–1.99)	1.33 (0.84–2.11)
1,500–1,999	59	96,546	1.24 (0.77–2.02)	1.32 (0.81–2.15)
≥2,000	15	21,734	1.49 (0.78–2.85)	1.53 (0.80–2.95)
p trend			*0.30*	*0.24*

[1]RR adjusted for age and trial intervention group.–[2]RR adjusted for age, trial intervention group, physical activity at work (not working, very light, light, moderate and heavy) and at leisure (light, moderate and heavy), history of Type II diabetes, family history of prostate cancer, height (<169, ≥169 to <172, ≥172 to <176, ≥176 to <179 and ≥179 cm), BMI (<22.5, ≥22.5 to <25, ≥25 to <27.5, ≥27.5 to <30, ≥30 to <32.5 and ≥ 32.5 kg/m^2), smoking inhalation (never/seldom, often and always), total number of cigarettes/day (<10, ≥10 to <20, ≥20 to <40, and ≥40), marital status (currently married), education (university degree, some vocational training, high school graduate and primary school or less), urban residence (≤50,000 inhabitants or >50,000 inhabitants) and total energy intake (continuous).–[3]Data on stage was available for 862 cases (561 nonadvanced; 301 advanced cases).–[4]Data on grade was available for 817 cases (626 low grade; 191 high grade cases).

The values inside parentheses indicate (95% CI).

These covariates were chosen because they have been reported to be prostate cancer risk factors or because they confounded the associations in our analysis. Dietary vitamin D or dairy fat did not materially alter the calcium-prostate cancer association and were therefore not included in the models. Adding lycopene, total fat, fish, selenium, red meat, vitamin E and alcohol to the multivariate model also did not change the results appreciably.

Effect modification was examined by additionally including a cross-product term of calcium or dairy food intake (modeled as continuous variables) and the covariate of interest. The assumption of constant risk for proportional hazards, tested by examining the cross-product term of follow-up time and the variable of interest, was met for all exposure variables and all covariates. All *p* values were two-sided and statistical analyses were performed using the Statistical Analysis Systems (SAS) release 8.2 (SAS Institute, Cary, NC).

Results

Table I shows selected age-standardized study participant characteristics according to increasing levels of energy-adjusted dietary calcium intake. In general, men with high dietary calcium intakes were slightly older, had a higher BMI, and personal history of diabetes, and they were less likely to live in an urban area, were not as highly educated, and were physically less active at work than men with low calcium intakes. In addition, men with high calcium intakes consumed more total fat, phosphorus, selenium, dairy products, dairy fat and total energy, and they consumed less lycopene, fish, red meat, alcohol, dietary vitamin D and E than men with low calcium intakes. The correlation coefficients between calcium and total dairy products, phosphorus, vitamin D and dairy fat were 0.90, 0.86, 0.21 and 0.56, respectively. The correlation coefficients between dietary calcium and individual dairy products were 0.24 for butter, 0.46 for whole milk, 0.40 for low fat milk, 0.10 for ice cream, 0.07 for cream, 0.43 for cheese and 0.35 for sour milk products.

We observed a strong, graded, positive association between calcium intake and total prostate cancer risk (Table II). The multivariate RR across increasing categories of dietary calcium intake (<1000, 1000–1499, 1500–1999 and ≥2000 mg/day) were 1.00, 1.28, 1.38 and 1.63 (95% CI, 1.27–2.10; *p* trend < 0.0001). The multivariate risks for calcium were virtually unchanged after controlling for calcium-adjusted phosphorus intake (for the highest *versus* lowest dietary calcium intake category, RR= 1.58; 95% CI, 1.19–2.11; *p* trend = 0.002).

When we stratified our analyses by method of case detection, we observed a 50% increased risk comparing extreme categories (95% CI, 1.03–2.19; *p* trend = 0.01) for cases that were detected through symptoms, and a 43% increased risk, though not statistically significant (95% CI, 0.85–2.39; *p* trend = 0.45) for the rest of the cases. When we analyzed dietary calcium intake in relation to nonadvanced, advanced, high grade and low grade prostate cancer, similar associations to total prostate cancer were observed (Table II). The multivariate model showed a 59% increased risk of nonadvanced

TABLE III – RELATIVE RISK (95% CI) OF TOTAL PROSTATE CANCER IN RELATION TO CALCIUM FROM DAIRY PRODUCTS, DAIRY FAT AND INDIVIDUAL DAIRY PRODUCTS INTAKE

Calcium from dairy or dairy food item (quintiles)	Median intake (g/d)	Cases	Person-years	Multivariate model RR[1]	Multivariate model RR[2]
Calcium from dairy					
Q1	565.8	221	68,961	1.0	–
Q2	870.2	262	67,451	1.18 (0.99–1.42)	–
Q3	1066.0	245	66,964	1.12 (0.93–1.34)	–
Q4	1274.1	270	66,438	1.23 (1.03–1.47)	–
Q5	1613.7	269	65,769	1.28 (1.07–1.54)	–
p trend				*0.008*	–
Dairy fat					
Q1	26.6	236	68,788	1.0	1.0
Q2	45.7	253	67,675	1.08 (0.90–1.29)	1.05 (0.87–1.25)
Q3	59.6	233	67,542	0.96 (0.80–1.16)	0.93 (0.77–1.12)
Q4	72.1	256	65,826	1.07 (0.89–1.28)	1.02 (0.85–1.22)
Q5	90.0	289	65,753	1.20 (1.00–1.43)	1.12 (0.93–1.34)
p trend				*0.08*	*0.30*
Toal dairy					
Q1	380.9	221	69,572	1.0	1.0
Q2	633.8	269	67,630	1.23 (1.03–1.48)	1.07 (0.86–1.32)
Q3	798.5	258	67,237	1.18 (0.99–1.42)	0.98 (0.78–1.23)
Q4	962.7	262	66,112	1.20 (1.00–1.45)	0.93 (0.73–1.19)
Q5	1220.2	257	65,034	1.26 (1.04–1.51)	0.87 (0.66–1.14)
p trend				*0.03*	*0.17*
Total milk					
Q1	152.6	246	69,567	1.0	1.0
Q2	362.9	246	67,329	1.0 (0.84–1.20)	0.94 (0.79–1.13)
Q3	544.3	265	66,828	1.08 (0.91–1.29)	0.97 (0.80–1.17)
Q4	725.2	261	66,145	1.09 (0.91–1.30)	0.94 (0.77–1.14)
Q5	993.5	249	65,715	1.08 (0.91–1.30)	0.86 (0.70–1.07)
p trend				0.25	0.21
Whole milk[3]					
Q1	0	253	70,411	1.0	1.0
Q2	27.0	256	68,880	0.98 (0.81–1.18)	0.97 (0.80–1.17)
Q3	97.5	253	66,690	0.96 (0.78–1.19)	0.96 (0.78–1.19)
Q4	319.3	260	64,596	1.02 (0.84–1.25)	0.98 (0.81–1.19)
Q5	667.9	245	65,007	1.05 (0.86–1.29)	0.93 (0.76–1.13)
p trend				*0.43*	*0.53*
Low fat milk[3]					
Q1	75.9	213	68,478	1.0	1.0
Q2	156.5	278	66,430	1.27 (1.06–1.52)	1.24 (1.03–1.49)
Q3	245.9	241	65,347	1.08 (0.89–1.31)	1.03 (0.85–1.25)
Q4	421.9	281	66,939	1.25 (1.04–1.51)	1.14 (0.95–1.38)
Q5	773.1	254	68,389	1.18 (0.97–1.44)	1.00 (0.81–1.23)
p trend				*0.15*	*0.44*
Butter					
Q1	5.1	238	68,376	1.0	1.0
Q2	24.2	258	67,409	1.08 (0.90–1.29)	1.07 (0.90–1.29)
Q3	39.6	279	66,991	1.17 (0.97–1.39)	1.15 (0.96–1.38)
Q4	52.2	246	66,163	1.02 (0.85–1.22)	1.02 (0.85–1.23)
Q5	71.7	246	66,645	1.00 (0.84–1.20)	1.04 (0.87–1.25)
p trend				*0.83*	*0.84*
Ice cream					
Q1	0	260	67,137	1.0	1.0
Q2	0.5	247	66,045	0.91 (0.75–1.09)	0.91 (0.75–1.09)
Q3	1.6	253	65,340	0.93 (0.76–1.13)	0.93 (0.76–1.13)
Q4	3.4	250	68,040	0.88 (0.72–1.06)	0.88 (0.73–1.07)
Q5	9.3	257	68,963	0.90 (0.75–1.08)	0.90 (0.75–1.08)
p trend				*0.41*	*0.43*
Cream					
Q1	1.2	237	66,354	1.0	1.0
Q2	4.8	248	66,707	0.95 (0.78–1.14)	0.95 (0.79–1.15)
Q3	7.4	215	67,211	0.81 (0.66–1.00)	0.83 (0.67–1.01)
Q4	11.2	258	68,647	0.94 (0.77–1.15)	0.97 (0.79–1.18)
Q5	47.7	309	66,666	1.09 (0.91–1.30)	1.11 (0.93–1.33)
p trend				*0.02*	*0.01*
Cheese					
Q1	3.0	231	66,231	1.0	1.0
Q2	11.3	223	65,815	0.93 (0.77–1.13)	0.91 (0.75–1.10)
Q3	18.0	282	67,939	1.16 (0.96–1.39)	1.13 (0.94–1.36)
Q4	28.4	249	67,833	1.01 (0.84–1.22)	0.97 (0.80–1.18)
Q5	54.6	282	68,767	1.13 (0.95–1.36)	1.04 (0.86–1.25)
p trend				*0.11*	*0.59*

TABLE III – RELATIVE RISK (95% CI) OF TOTAL PROSTATE CANCER IN RELATION TO CALCIUM FROM DAIRY PRODUCTS, DAIRY FAT AND INDIVIDUAL DAIRY PRODUCTS INTAKE (CONTINUED)

Calcium from dairy or dairy food item (quintiles)	Median intake (g/d)	Cases	Person-years	Multivariate model RR[1]	Multivariate model RR[2]
Sour milk products					
Q1	0	240	68,607	1.0	1.0
Q2	31.3	256	66,582	1.07 (0.89–1.29)	1.05 (0.87–1.27)
Q3	79.7	250	67,301	1.03 (0.86–1.24)	0.99 (0.82–1.19)
Q4	193.0	267	66,924	1.08 (0.90–1.29)	1.01 (0.84–1.22)
Q5	423.1	254	66,170	1.07 (0.90–1.28)	0.97 (0.81–1.22)
p trend				*0.54*	*0.60*

[1]Multivariate model as in Table II.–[2]Multivariate model with additional adjustment for dietary calcium.–[3]With additional adjustment for each other.The values inside parentheses indicate (95% CI).

prostate cancer comparing the top to bottom categories of calcium intake (p trend = 0.03). Increased RR estimates were also seen for advanced prostate cancer but did not quite reach statistical significance because of a limited number of advanced cases (p trend = 0.23). After stratification by grade, the multivariate model showed a 43% increased risk for low grade tumors comparing extreme categories of intake (p trend = 0.10) and a 53%, though not statistically significant increased risk for high grade tumors (p trend = 0.24).

Excluding the first 5 years of follow-up also gave similar results, with the multivariate RR of total prostate cancer for ≥2000 mg/day compared to <1000 mg/day of calcium intake being 1.69 (95%CI, 1.29–2.22; p trend = 0.0002). To address the potential for increased exposure misclassification over time, we divided the follow-up time into an earlier (1985–1994) and later (1995–2002) period. The association between dietary calcium intake and prostate cancer was slightly stronger in the later (the multivariate RR comparing ≥2000 *vs.* <1000 mg/day was 1.67; 95% CI, 1.24–2.26) than in the earlier follow-up period (multivariate RR, 1.42 (95% CI, 0.89–2.26), suggesting no increased exposure misclassification over time.

Similar findings were observed when we repeated the analysis using quintiles (multivariate RR for top *versus* bottom quintile, 1.28; 95% CI, 1.04–1.58). When we repeated our analysis using 700 mg/day as the low cut point, the multivariate RR of total prostate cancer across increasing categories of calcium intake (<700, 700–999, 1000–1499, 1500–2000 and ≥2000 mg/day) were 1.0, 0.94, 1.22, 1.31 and 1.55 (95% CI, 1.07–2.25; p trend = 0.002). Using calcium intake of <1200 mg/day as the reference category (which corresponds to the recommended daily calcium intake in the U.S.), the multivariate RR of total prostate cancer for men with ≥1200 mg calcium intake per day was 1.17 (95%, 1.04–1.33; p = 0.01). When we considered dietary calcium intake as a continuous variable in a multivariate model, the RR of total prostate cancer associated with a 500 mg/day increment in calcium intake was 1.18 (95% CI, 1.09–1.27). In this cohort, 11% of participants reported using calcium supplements and the latter contributed only 2% to total calcium intake. When compared with men not using calcium supplements, the multivariate RR of total prostate for intake of greater than zero mg/day of calcium from supplements was 0.96 (95% CI, 0.81–1.15).

We found an increased risk of total prostate cancer for higher intake of calcium from total dairy (Table III). The multivariate RRs of total prostate cancer across increasing quintiles of intake were 1.00, 1.18, 1.12, 1.23 and 1.28 (95% CI, 1.07–1.54; p trend = 0.008). There was no significant association of calcium from total dairy by stage or grade of prostate cancer (data not shown). There was a marginally statistically significant increased risk of prostate cancer with increased levels of dairy fat (multivariate RR comparing extreme quintiles, 1.20, 95% CI, 1.0–1.43; p trend = 0.08), which was stronger in advanced disease (RR, 1.45; 95% CI, 1.0–2.09) (Table III). This association was no longer significant after controlling for dietary calcium (p trend = 0.30).

We found an increased risk of total prostate cancer for higher intake of total dairy products (Table III). The multivariate RR of total prostate cancer across increasing quintiles of total dairy products intake were 1.00, 1.23, 1.18, 1.20 and 1.26 (95% CI, 1.04–1.51; p trend = 0.03). After further control for dairy fat, the association was similar (RR for top *versus* bottom level of intake, 1.22; 95% CI, 1.01–1.48; p trend = 0.09). However, when we controlled for dietary calcium or calcium from dairy products, the association was attenuated and became statistically nonsignificant (the multivariate RR for the highest *versus* lowest quintile were 0.87 (95% CI, 0.66–1.14); p trend = 0.17, and 1.0 (95%CI, 0.73–1.37; p trend = 0.81), respectively). No significant association between total dairy product intake and prostate cancer risk was observed in any subgroup defined by prostate cancer stage or grade (data not shown). We found no clear association for individual dairy foods and prostate cancer risk (Table III). However, there was a nonsignificant increased risk for low fat milk consumption after multivariate adjustment including adjustment for whole milk intake (RR comparing extreme quintiles, 1.18; 95% CI, 0.97–1.44; p trend = 0.15). When we adjusted for calcium, the multivariate risk comparing extreme quintiles of low fat milk was 1.0 (95% CI, 0.81–1.23; p trend = 0.44). There was a significant trend for a positive association between consumption of cream and total and advanced prostate cancer that remained statistically significant after additional adjustment for dairy fat and calcium (p trend ≤ 0.05). However, none of the point estimates for cream intake was statistically significant.

Phosphorus intake showed a nonsignificantly increased risk with total prostate cancer risk (multivariate RR comparing extreme quintiles, 1.17; 95% CI, 0.97–1.40). The association remained virtually unchanged after controlling for phosphorus-adjusted calcium intake (for top *versus* bottom quintiles RR, 1.10; 95% CI, 0.91–1.33). This was similar for nonadvanced, advanced, low grade and high grade prostate cancer (data not shown). We detected no relation of vitamin D to total, nonadvanced, advanced, low grade or high grade prostate cancer risk. The multivariate risk estimates comparing extreme quintiles of vitamin D intakes (≥7.4 *vs.* ≤ 3.2 μg/day) were 0.87 (95% CI, 0.73–1.04), 0.93 (95% CI, 0.72–1.21), 0.81 (95% CI, 0.57–1.17), 0.88 (95% CI, 0.68–0.1.14) and 0.78 (95% CI, 0.50–0.1.22), respectively. When the analyses were controlled for calcium intake, the risk estimates did not change materially (data not shown).

The associations between intakes of calcium or dairy products and total, nonadvanced, advanced, low grade and high grade prostate cancer did not vary across subgroups of men defined by age, trial intervention group, physical activity, family history of prostate cancer, history of type II diabetes, height, body-mass index, smoking, marital status, education, urban residence, and intakes of total energy, dairy fat, vitamin D and phosphorus (all p interaction > 0.05).

Discussion

The findings from this large prospective study suggest that high intake of dietary calcium or calcium from dairy products is related to increased risk of prostate cancer. Increased consumption of

dairy products and dairy fat showed no relation with risk after adjusting for calcium.

Results from previous epidemiologic studies that have examined calcium intake in relation to prostate cancer have been inconsistent. Specifically, 6[14,24–28] of 8 case-control studies[5,14,24–29] showed no association between the two, 1 study reported a statistically significant increased risk[5] and 1 study reported an inverse association,[29] although that study was relatively small in size (n = 100 cases). In contrast, 5[6,7,9,11,13] of 7 cohort studies[6,7,9,11,13,16,30] showed a positive association with higher calcium intake, whereas the remaining 2 studies found no association.[16,30] In the Health Professionals Follow-up study, Giovannucci *et al.* showed that calcium from dietary and from supplemental sources both independently increased the risk of advanced prostate cancer.[7,8] A recent meta-analysis synthesizing the findings from 6 of the previous prospective studies and 7,154 prostate cancer cases reported an increased risk of prostate cancer with high *versus* low calcium intake (RR, 1.39; 95% CI, 1.09–1.77).[4]

Findings from previous studies on dairy or milk intake in relation to prostate cancer risk are also inconsistent. Specifically, 7[5,31–36] of 15 case-control studies[5,24,25,31–42] and 6[6,8–10,12,13] of 15 prospective studies[6,8–13,16,30,43–48] showed a significantly increased risk of prostate cancer with high dairy or milk consumption, while the remaining studies reported no association.[11,16,30,43–48] Two recent meta-analyses including 11 of the previous case-control (n = 2,929 cases) and 10 of the previous prospective studies (n = 8383 cases) reported pooled risk estimates for total dairy product intake of 1.68 (95% CI, 1.32–2.12)[49] and 1.11 (95% CI, 1.00–1.22),[4] respectively.

Although biologic measures of vitamin D have been suggested to lower prostate cancer risk in some studies,[50] data based on dietary measures of vitamin D are less consistent. Similar to previous dietary studies,[5,8,11,13,14,16] we did not observe a relation of dietary vitamin D to prostate cancer risk. Dietary intake of vitamin D is usually a poor measure of total vitamin D because humans derive vitamin D from sunlight exposure in addition to dietary intake.[51]

In our study, phosphorus intake showed overall null results in relation to prostate cancer risk. In a recent study by Giovannucci *et al.*,[7] phosphorus was not associated with advanced or fatal prostate cancer but there was a suggestive increase in risk for high grade prostate cancer with high phosphorus intakes after adjusting for calcium. Other previous studies suggest an attenuation of a previously observed increased risk after adjustment for calcium but none of the results were statistically significant.[8,13,16] Our previous report[16] from the ATBC study suggested a weak interaction between phosphorus and calcium in relation to prostate cancer risk (with low calcium and high phosphorus lowering risk) (p interaction = 0.09). However, the current analysis, which includes over 1,000 additional cases, did not find evidence of a stronger interaction (p interaction = 0.11). Two other studies also found no significant interaction between calcium, phosphorus and prostate cancer risk,[5,8] whereas 1 small prospective study showed that the relation of calcium to prostate cancer was stronger among men with low phosphorus levels (p interaction = 0.02).[9]

In the current study, we found an increased risk of prostate cancer for calcium from dairy products and a similar association with total dairy products. However, the association of the latter was no longer evident after adjustment for calcium. Similar to our study, 3 studies reported an attenuation of the association between total dairy intake and prostate cancer after adjustment for calcium.[9,13,44] Although this implies that dairy product consumption may influence prostate carcinogenesis *via* a high calcium intake, the high correlation between calcium and dairy products makes it difficult to fully discern the independent effect of the 2 on prostate cancer risk.

The suggestive positive relation between dairy fat and prostate cancer seen in our study was not independent of calcium. We were unable to identify individual dairy foods responsible for increased risk of prostate cancer although suggestive positive relations were observed for intakes of 2 rather different dairy food items, low fat milk and cream. The latter showed a positive relation with increasing levels of intake and prostate cancer that persisted after adjustment for calcium, dairy fat or simultaneous adjustment for both. However, none of the point estimates was statistically significant. Only 1 recent study[13] has examined the effect of cream yielding no significant results. It is possible that other compounds specific to cream are responsible for this association and future studies should address this possibility. The suggestion of a positive relation between low fat milk and prostate cancer risk is compatible with a positive relation with the nonfat component of dairy. Three studies have also shown increased risk of prostate cancer with skim milk or low-fat milk.[6,13,48] However, when we adjusted for calcium, the association with low fat milk was not independent of calcium.

A potential mechanism that may explain the elevated risk of prostate cancer seen with increased dietary calcium intake involves the suppression of the active form of vitamin D 1,25 (OH)2D by high levels of calcium.[52,53] The active form of vitamin D that is synthesized by both the kidney and the prostate exerts several biological effects upon its interaction with the vitamin D receptor (VDR).[54] This interaction initiates a complex cascade of events and influences the rate of RNA polymerase II-mediated transcription of genes involved in apoptosis, proliferation and angiogenesis.[55]

One strength of our study is its prospective design, which essentially rules out recall bias. The use of a validated food use questionnaire with a color picture booklet of portion sizes likely reduced the level of misclassification of food composition. Furthermore, we had virtually complete prostate cancer case ascertainment and a long follow-up period, which yielded a substantial number of cases, thereby ensuring ample statistical power to detect associations. The high dairy/milk consumption in Finland also provides the ideal setting for exploring associations between dairy products/calcium and prostate cancer.

A further strength of our study is that population-based prostate-specific antigen (PSA) screening programs have not yet been widely adopted in Finland. Therefore, a large proportion of cases in our study were detected as a result of clinical symptoms. This lessens the possibility that our results are influenced by detection bias. In contrast, contemporary prostate cancer studies conducted in the U.S. may be particularly vulnerable to PSA-related detection bias.[56] As a consequence, previous studies that included large proportions of cases diagnosed in the PSA-era have reported stronger associations with calcium for more advanced disease than for the early, subclinical disease often detected through elevated PSA.[7,8,11,14]

There are 2 potentially distinct forms of detection bias associated with PSA-detected prostate cancers that can be differentiated. The first form of detection bias arises if calcium enhances risk of all types of prostate cancers to a similar degree but calcium intake varies according to prostate cancer screening behavior (*i.e.*, men with high intake of calcium would be more (or less) likely to undergo PSA tests).

The second form of detection bias arises if PSA-detected prostate cancers represent a particular subgroup of cancers that have no association or only a weak association with calcium, and calcium acts only on prostate cancer progression but not on prostate cancer initiation. In our study, the median calcium intake among prostate cancer cases diagnosed through screening was lower than the median calcium intake among cases detected through symptoms (1345.4 *vs.* 1416.5 mg/day), but the relation of calcium to prostate cancer risk did not vary according to the case-detection method, and results for calcium did not vary according to tumor stage or grade. This suggests that the positive relation of calcium to prostate cancer risk observed in our study is probably not caused by detection bias. Similar to our study, a recent US study that had most of its cases diagnosed before PSA screening[13] showed a statistically significant positive association between calcium intake and total prostate cancer risk.

Although our study population was composed of male smokers, our results are largely consistent with findings from previous prospective studies of dietary calcium that included both smokers and nonsmokers.[6,7,9,11,13] In addition, previous studies did not report effect modification of the calcium and prostate cancer association by smoking status. Thus, our results are likely generalizable to men who do not smoke. Smoking decreases intestinal calcium absorption,[57] a circumstance that may have led us to underestimate the true magnitude of the association between calcium and prostate cancer risk in our study.

Despite accumulating epidemiologic data showing that high intakes of calcium may increase prostate cancer risk, the potential risks need to be balanced with the potential benefits of calcium for osteoporosis, and possibly also hypertension, insulin resistance and colon cancer.[58–61] Some data indicate a protective effect on colon cancer from 1 glass of milk per day[59] while results from the Women's Health Initiative suggest little benefit of calcium for colorectal cancer and hip fractures.[62,63] Our data suggest that the current recommended dietary allowance (RDA) of 1,200 mg/day of calcium for men aged 50 or over[64] (equivalent to 2–3 glasses of milk per day) may exceed the optimal amount needed to achieve a balance between the apparent health benefits and risks of calcium.

In conclusion, the findings from this large prospective study suggest that high intake of calcium is related to increased risk of prostate cancer. Given calcium's other potential health benefits, further research is needed to determine the risk-benefit trade-offs associated with dietary intake of calcium. Although the positive association seen with total dairy products was no longer apparent after controlling for calcium, an independent role for some ingredient other than calcium present in individual dairy products cannot be completely excluded. Further clarification of the role of non-calcium components of dairy products in relation to prostate cancer risk is warranted.

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